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Signed A. Mahoney

Dated 14 September 1999

Patents Form 1/77

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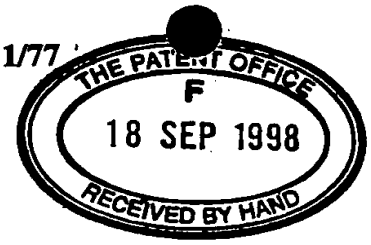

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1/77

21SEP98 E391375-1 D02029
P01/7700 25.00 - 9820405.0

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — AJB/PS/P32147

2. Patent application number
(The Patent Office will fill in his part)

18 SEP 1998 — **9820405.0**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

SMITHKLINE BEECHAM PLC
NEW HORIZONS COURT, BRENTFORD,
MIDDLESEX TW8 9EP

Patents ADP number *(if you know it)*

5800974002

If the applicant is a corporate body, give the country/state of its incorporation

UNITED KINGDOM

4. Title of the invention — Process

5. Name of your agent *(if you have one)*

CORPORATE INTELLECTUAL PROPERTY

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

SMITHKLINE BEECHAM PLC
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP

Patents ADP number *(if you know it)*

4471231005

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	0
Description	4
Claim(s)	2
Abstract	0
Drawings	1

10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 1/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature Alison Blakey Date 18-Sep-98

A J Blakey

12. Name and daytime telephone number of person to contact in the United Kingdom

A J Blakey 01279 644355

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Notes

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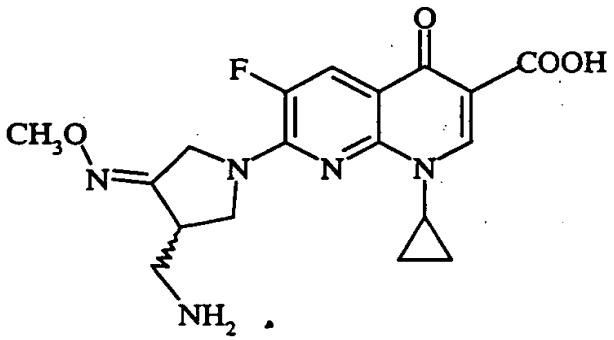
f) For details of the fee and ways to pay please contact the Patent Office.

PROCESS

The present invention relates to a process for the production of a quinoline(naphthyridine)carboxylic acid derivative having antibacterial activity.

EP 688772 discloses novel quinoline(naphthyridine)carboxylic acid derivatives, including anhydrous (R,S)-7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid of formula I, having antibacterial activity.



I

PCT/KR98/00051 discloses (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate and hydrates thereof including the sesquihydrate (the 'methanesulfonate sesquihydrate').

PCT/KR98/00051 discloses a process for the production of the methanesulfonate sesquihydrate comprising reaction of the free base with methanesulfonic acid in dichloromethane / ethanol followed by recrystallisation of the resulting crude salt anhydrate from either water : acetone (10:7 v/v), or water : ethanol (1:2 v/v). The overall yield for this two step process is 70-80%. An alternative process for the production of the methanesulfonate sesquihydrate described in PCT/KR98/00051 comprises exposing a solvate of the methanesulfonate (ethanol 0.11%) to high relative humidity (nitrogen >93% humidity).

The present invention relates to an improved process for the production of the methanesulfonate sesquihydrate which comprises direct salt and hydrate formation.

According to the invention there is provided a process for the production of 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate

which comprises reacting 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid and methanesulfonic acid in a solvent comprising at least one C_{1-8} alcohol and water, and isolating the resulting solid product.

The 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (hereinafter referred to as 'the free base') used in the process of the invention may be prepared as described in EP 688772.

Suitable alcohols for use in the process of the invention include C_{1-4} alcohols and mixtures thereof, e.g. methanol, ethanol and propanol; the preferred C_{1-8} alcohol is isopropanol.

In addition to at least one C_{1-8} alcohol and water the solvent may contain other components, such as C_{1-4} haloalkanes. However, the solvent preferably comprises essentially of at least one C_{1-8} alcohol and water.

Suitable ratios of alcohol : water for use in the process of the invention include ratios in the range 10:1 to 1:1 v/v, a particularly suitable ratio of alcohol : water is 2:1 v/v.

Any suitable ratio of free base to solvent may be used, for example, a ratio of up to 1:100 w/v.

The process of the invention may use 0.7 to 1.5 equivalents of methanesulfonic acid, preferably 1.0 equivalents of methanesulfonic acid.

The mixture of the free base and methanesulfonic acid may be warmed in the solvent to aid dissolution. On cooling the methanesulfonate sesquihydrate will crystallise out of solution. To aid crystallisation the solution may be seeded with a small quantity of solid methanesulfonate sesquihydrate. In order to obtain polymorphically pure methanesulfonate sesquihydrate it is preferable that seeding of the solution is completed before crystallisation begins. Seeding of the crystallisation solution is preferably performed at a temperature $\geq 25°C$, for example at a temperature of about 30°C.

The process of the invention may be used to produce racemic methanesulfonate sesquihydrate or may be used for the production of enantiomerically enriched or enantiomerically pure methanesulfonate sesquihydrate, using racemic or enantiomerically enriched or enantiomerically pure free base. Enantiomerically

enriched or enantiomerically pure free base may be prepared by resolution of the racemic free base, e.g. by chiral HPLC.

The process according to the invention has the advantage that direct salt formation eliminates one step in the synthesis and gives a high yield of high purity methanesulfonate sesquihydrate. In turn these advantages result in improved throughput and savings in labour and materials costs during manufacture.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The invention is illustrated by the following examples. However, it should be understood that the examples are intended to illustrate but not in any manner limit the scope of the invention.

Example 1

To a suspension of (R,S)-7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (20.00 g, 51.4 mmol) in isopropanol (120 ml) and water (60 ml) was added methanesulfonic acid (3.300 ml, 50.9 mmol) at 38-40°C. The resultant dark brown solution was stirred for 15 min after which time charcoal (6.00 g of Darco G-60) was added. The suspension was stirred at 38-40°C for 4h then filtered. The filtrate was allows to cool to 30°C and seed crystals of (R,S)-7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate (15 mg) added. A precipitate began to form within 15 min. The suspension was allowed to cool to 20-23°C over 90 min and was stirred for 36h. The slurry was cooled to 0-5°C for 60 min then filtered and washed with isopropanol (50 ml and 44 ml). The product was sucked dry for 30 min and then further dried at 50-55°C under vacuum. ~~The dried product was exposed to the atmosphere for 18h to give the methanesulfonate~~ sesquihydrate 21.29 g (85%), purity >99.5% by HPLC.

The X-ray diffraction pattern of the methanesulfonate sesquihydrate was measured as follows:

Diffractometer type:	PW1710 BASED
Tube anode:	Cu
Generator tension [kV]:	40
Generator current [~~m~~A]:	30

Wavelength Alpha1 [Å]:	1.54060
Wavelength Alpha2 [Å]:	1.54439
Intensity ratio (alpha1/alpha2):	0.500
Divergence slit:	AUTOMATIC
Irradiated length [mm]:	12
Receiving slit:	0.1
Spinner:	ON
Monochromator used:	YES
Start angle [°2θ]:	3.500
End angle [°2θ]:	35.000
Step size [°2θ]:	0.020
Maximum intensity:	2970.250
Time per step [s]:	2.300
Type of scan:	STEP
Minimum peak tip width:	0.10
Maximum peak tip width:	1.00
Peak base width:	2.00
Minimum significance:	0.50

The X-ray diffraction pattern of the methanesulfonate sesquihydrate is shown in Figure 1. The compound shows characteristic peaks at 2θ = 8.2, 12.2 and 14.6°.

CLAIMS

1. A process for the production of 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate which comprises reacting 7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid and methanesulfonic acid in a solvent comprising at least one C_{1-8} alcohol and water and isolating the resulting solid product.

2. A process according to claim 1 wherein the alcohol is a C_{1-4} alcohol.

3. A process according to claim 2 wherein the alcohol is isopropanol.

4. A process according to any one of the preceding claims wherein the ratio of alcohol : water is in the range 10:1 to 1:1 v/v.

5. A process according to claim 4 wherein the ratio of alcohol : water is 2:1 v/v.

6. A process according to any one of the preceding claims wherein the ratio of 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid : solvent is up to 1:100 w/v.

7. A process according to any one of the preceding claims which uses 0.7 to 1.5 equivalents of methanesulfonic acid.

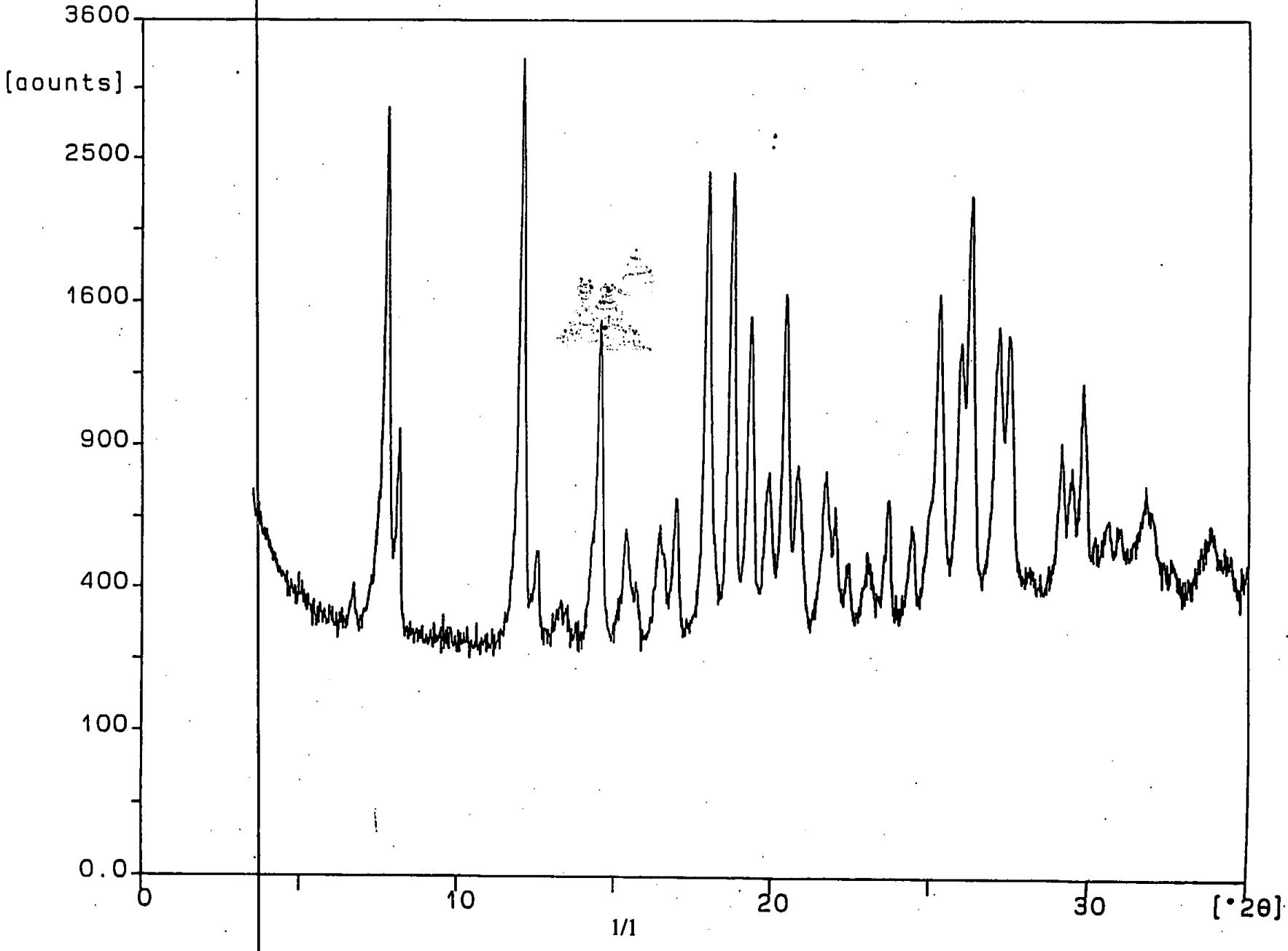
8. A process according to any one of the preceding claims wherein the recrystallisation solution is seeded with a small quantity of 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate to aid crystallisation.

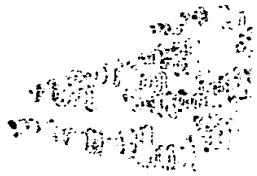
9. A process according to claim 8 wherein the solution is seeded whilst at a

temperature of ≥ 25°C.

10. A process according to claim 9 wherein the solution is seeded whilst at a temperature of 30°C.

FIGURE 1





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